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The differential diagnosis of pulmonary embolism (PE) is broad and includes many life-threatening illnesses that must be identified promptly to intervene appropriately. These high-stakes alternatives include myocardial infarction, pneumonia, pneumothorax, and sepsis, among other illnesses. The physician has the difficult task of narrowing the differential list to the correct illness. The more quickly this is done, the more likely it is that definitive treatment can be initiated in time to save the patient.

The most difficult step in treating a patient who has PE is identifying the patient who requires treatment. Multiple options are available for treating a patient with known PE, some of which demonstrate significant changes from past practice. Treatment of PE has become more refined during the past few years, with the applicability of thrombolytics and the availability of low molecular weight heparins arising as exciting developments in the field. Other time-tested treatments, such as unfractionated heparin and surgically placed filters, still have significant roles.

The emergency physician is in the unique position of seeing many patients in whom PE can be prevented. As the commonly used portal to inpatient service, emergency physicians are able to address the treatments that can prevent this life-threatening illness in patients who will be hospitalized for other reasons. Preventing PE in a high-risk patient can be a lifesaving intervention.

Part one of this two-part series addressed the epidemiology, clinical presentation, and the appropriate use of diagnostic studies to identify those with PE. Unfortunately, no one exam is perfect in detecting PE. The exams assessing for PE, the clinical exam, and the exams that eliminate or identify other illnesses on the differential list can be used in combination. This is the most effective way to approach a patient with possible PE.

This second and final part of the series covers the topics of differential diagnosis that must be considered when a patient presents with symptoms consistent with PE, treatment, and considerations for prevention of this disease state.

—The Editor

Pulmonary Embolism: Recent Advances in Diagnosis and Treatment Modalities

Part II — Differential Diagnoses

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Differential Diagnosis

PE can present with a wide range of severity. Patients may present in a premorbid state of severe shock, with the differential diagnosis including all of the elements of the shock differential. The symptoms of PE in a stable patient with small emboli may be so protean and vague that they elicit a wide-ranging differential diagnosis for the presenting symptom, whether it is chest pain, respiratory difficulties, low-grade fever, or a feeling of anxiety. *(See Table 1.)* Certainly, the symptoms alone of chest pain and shortness of breath immediately bring to mind a varied group of illnesses, many of which are life-threatening. The advantage of obtaining many of the tests that are not specific for PE is that they may identify an alternate diagnosis. It is important to distinguish diagnoses on the differential that contraindicate the use of anticoagulation as treatment for PE, such as pericarditis or aortic dissection.[1]

A patient in shock from a large embolus presents as a patient who is hypotensive with possible respiratory difficulties. Up to 8% of patients with PE present in extremis.[2,3] The differential in this patient can include sepsis or shock from pump failure perhaps due to a myocardial infarction or severe congestive heart failure (CHF). Hemorrhagic shock also can present in this way. Neurogenic shock and anaphylactic shock are likely to present with other clinical scenarios. Treatment for these illnesses does have some similarities, such as airway control and blood pressure support, but there are some significant differences. As discussed in the first part of this series, the electrocardiogram (ECG) and chest x-ray are exams with low sensitivity and specificity for PE. Their usefulness in identifying and excluding other life-threatening illnesses, however, is essential to providing appropriate care. When a large myocardial infarction (MI) is discovered on the ECG of a patient with shock, definitive treatment can begin. If CHF or pneumonia is found on the chest x-ray, diuretics, antibiotics, or other appropriate, specific treatment can start. It is important to remember that the patient who presents in shock with a mostly normal ECG and normal or nearly normal chest x-ray may well have PE and needs further workup to evaluate the possibility.

The differential of the less acutely ill patient is broad. Symptoms such as dyspnea and/or chest pain can suggest illnesses that are primarily pulmonic in origin, such as asthma, pleurisy, pneumonia, or pneumothorax. Chest pain as the primary complaint can bring to mind cardiac ischemia, pericarditis, aortic dissection, pulmonary disease, or musculoskeletal pain. Patients presenting with tachypnea can have any of these above illnesses, but metabolic acidosis and anxiety also must be considered. Of course, thrombus is not the only possible source for emboli. Fat may embolize from a fracture, air may embolize during a procedure, bullets or other foreign bodies may embolize, and pregnancy allows for the possibility of amniotic fluid embolism. These emboli may present similarly to a thrombotic embolism, but the treatment will differ because anticoagulation will not cure any of these other types of emboli.

Because the differential diagnosis list is extensive and broad, it is imperative that the physician assess an individual patient's risk for thromboembolic disease and consider it in the diagnostic workup of symptomatic patients, as described in part one of this article. It also is important to realize that it may be easy to dismiss a patient who appears anxious with complaints of dyspnea or chest pain once the other dangerous diagnoses are excluded, but the small PEs that may be causing these symptoms are a sign that a larger, life-threatening PE may be in the patient's near future unless prevented by the astute physician.

Treatment Options

Once the difficult task of determining that a patient needs treatment for PE has been accomplished, different treatment options may be considered. The first task in treatment is to deter-

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Table 1. Differential Diagnosis of Patient with Symptoms of Pulmonary Embolism

- Shock—cardiogenic, septic, neurogenic, anaphylactic, hemorrhagic
- Aortic dissection
- Pneumonia
- Pleurisy
- Pneumothorax
- Asthma
- Congestive heart failure
- Pericarditis
- Acute myocardial infarction
- Other emboli (i.e., fat, air, amniotic fluid, bullet)
- Anxiety attack
- Musculoskeletal pain
- Costochondritis
- Metabolic acidosis
- Angina

mine whether the current clot burden is such that immediate measures must be taken to remove the clot, either chemically through thrombolysis or mechanically via embolectomy. Once that decision is made, consideration must be given to anticoagulation, either as primary therapy or as prevention against future emboli. The choices among the anticoagulants include unfractionated heparin (UFH), low molecular weight heparin (LMWH), and oral anticoagulation with warfarin. Long-term prevention of future emboli may be achieved with anticoagulation or with filters that prevent the clot from traveling centrally. Each of these options will be discussed fully in the following sections. At each juncture, it is essential to consider the patient's severity of illness as well as the indications and contraindications to each method of therapy. *(See Table 2.)*

Heparin and Unfractionated Heparin. Since the 1930s, the treatment of thromboembolic disease has been based on anticoagulation.[4] PE is a potentially fatal disease in which anticoagulant therapy has been shown to improve outcomes dramatically.[5,6] In 1960, Barrit and Jordan established, with the first randomized trial, that those who were anticoagulated clearly had an improvement compared to those who received placebo.[6]

Standard treatment for patients with venous thromboembolism had been hospital admission, with UFH given by intravenous (IV) infusion for 5-10 days. Oral anticoagulation is begun in the hospital overlapping with the UFH, and then continues for at least three months.[7-12] This has been the treatment plan for both DVT and PE. This treatment may not aid those with hemodynamic compromise on presentation quickly enough, but it was the only medical treatment available for a long time.

The usefulness of UFH in patients with PE is that it prevents further clot formation by accelerating the action of antithrombin III, allowing endogenous fibrinolysis to lyse the existing clot.[1] The heparin can be administered subcutaneously, but most often is administered intravenously.[1] Subcutaneous dosing can result in more erratic absorption of a medication that must be titrated carefully to be therapeutic. Achieving a therapeutic range quickly enough is one of the greatest concerns when deciding to use heparin for treatment of a patient with suspected PE. Patients who are anticoagulated adequately within the first 24 hours have better outcomes. It has been found that those who are anticoagulated adequately during that time period have a PE recurrence rate of only 4-6%, as opposed to a recurrence rate of 23% in those who are not anticoagulated in the first day.[13]

Dosing regimens have moved away from a standard dosing scheme with adjustments made over time according to laboratory exams used as a guidepost for titration. The suggested regimen now is one that is weight-based. First, a bolus is given with suggested doses ranging from 80 IU/kg to 150 IU/kg.[1,4] The bolus is followed by a drip that is begun at 18 IU/ kg. Activated partial thromboplastin (PTT) levels then are monitored every 4-6 hours, with the drip adjusted appropriately. The goal is for the PTT to be 1.5 times the control value.[4]

Anticoagulation is not an innocuous intervention, however. Disadvantages to using UFH include repeated lab work to check the level of anticoagulation frequently, required hospitalization of the patient, and a risk of bleeding. The frequency of major bleeding is 4% in those treated with continuous IV UFH with a weight-based dosage system for PE or DVT.[14] Intracranial bleeding, retroperitoneal bleeds, and gastrointestinal bleeds are considered major bleeds. Those at higher risk for bleeding include patients who have had surgery within the past 14 days and patients with a history of peptic ulcer disease, gastrointestinal tract bleeding, genitourinary tract bleeding, disorders predisposing to bleeding, major thrombotic stroke within the previous 14 days, or severe thrombocytopenia.[11,15] It is essential to identify patients who have diagnoses that would preclude the use of anticoagulation and to treat them with alternate means. *(See Table 3.)* The risk of bleeding also increases with age.[16] The risk of recurrent VTE with standard UFH treatment is 6.8%.[17] A particular advantage of heparin is that is safe for pregnant patients.

Low Molecular-Weight Heparins. LMWHs have been used in Europe for more than 10 years, although they are relatively new in the United States.[18] LMWHs differ from standard UFH in that they have greater bioavailability, a longer half-life, a more predictable anticoagulant response when administered subcutaneously in fixed doses, and a higher ratio of anti-factor Xa to anti-factor IIa activity.[19-22] These differences occur because the LMWHs bind less than UFH to plasma proteins, macrophages, and proteins released from activated platelets and endothelial cells.[23]

LMWHs, although often discussed as a group, are distinct compounds with different pharmacological profiles and dose regimens; it is uncertain whether the results obtained with one preparation can be extended to another.[5] *(See Table 4.)* The U.S. Food and Drug Administration (FDA) regards LMWHs as individual drugs that cannot be used interchangeably.[24] They are distinct entities that have the potential for clinically significant differences in safety and efficacy. The different LMWHs probably are equivalent for low-dose indications, such as venous thromboprophylaxism, but at higher doses the efficacy and safety differences cannot be excluded.[24] Since November 2000, there have been two LMWHs approved by the FDA for use in treating VTE in the United States: enoxaparin and tinzaparin.[1] In addition, dalteparin now is approved for treatment of DVT.[25] The longer half-life of LMWHs and the more predictable anticoagulant response make them suitable for subcutaneous administration without laboratory monitoring.[26-28] If it is determined that monitoring is needed in a particular patient, anti Xa levels can be measured,

Table 2. Low Molecular-Weight Heparin vs. Unfractionated Heparin

	ADVANTAGES	DISADVANTAGES
Low molecular-weight heparin	• Can be given via subcutaneous shot instead of intravenously. • Dosing is less frequent • Very effective treatment for many DVTs	• Not yet shown to be safe treatment for all patients with PE. • High cost • Bleeding risk
Unfractionated heparin	• Historically well-demonstrated to be an effective treatment for PE when dosed appropriately • Effect can be stopped quickly once the IV infusion is turned off. • Less expensive	• Requires many blood draws and lab work to make sure dose is appropriate. • Bleeding risk

although few labs conduct this exam.

Multiple studies now have demonstrated the safety and efficacy of LMWH treatment in properly selected patients with DVT,[21,29-33] as well as patient satisfaction with this treatment.[32] LMWHs have allowed the possibility of either abbreviated inpatient stays[35] or outpatient treatment of DVT.[29,32-34] Patients who are proper candidates for outpatient treatment of DVT should have normal vital signs, a low bleeding risk, and well-functioning kidneys. Their home situation must make administration of the medication practical. Monitoring of blood work and appropriate follow-up on an outpatient basis are required.[33]

A Canadian study compared costs of treatment with LMWH and UFA for DVT. The costs measured included hospitalization, travel, home care, medication, lab work, and lost productivity for the patient and caregiver. For patients with acute proximal DVT, the researchers found that treatment at home with LMWH was less costly than treatment in the hospital with UFH. They also found that this savings occurred without compromising clinical outcomes or the patients' quality of life.[30]

Are LMWHs safe and appropriate treatments for those with PE? There is no large, randomized study that has demonstrated that patients with symptomatic PE safely can be treated with LMWH as a bridge to further anticoagulation. As has been stated previously, PE presents with significant variation in severity, presumably linked to the amount of clot and the ability of the patient to compensate. PE has been found in 50% or more of patients with DVT.[17] Some studies have examined the treatment of PE with LMWH by evaluating patients with defined DVT and then looking for PE. Researchers then evaluated the resolution of the signs of PE on follow up V/Qs and found LMWH equal in efficacy to UFH.[1,5,26] Most of these patients were asymptomatic for PE.

Tinzaparin and enoxaparin are FDA approved for inpatient treatment of patients with DVT as the primary presentation of their thromboembolic disease who also are found to have PE.[1] Dalteparin is approved only for treatment of those with DVT.[25] Treatment success of patients with DVT and PE that is found incidentally cannot be assumed to correlate with treatment of patients with symptomatic PE.

Two studies specifically evaluated the use of LMWH as a treatment for symptomatic PE as a bridge to warfarin treatment. Patients with diagnosed PE who were not candidates for thrombolysis (the criteria for thrombolysis were not described in the studies) and had no contraindications to anticoagulation were treated with LMWH or UFH. One study group used reviparin and the other study used tinzaparin.[5,26] Both studies concluded that the LMWH was as safe and effective in treating PE as UFH when used as delineated in the study. The patients remained in the hospital for their treatment. No statement about outpatient treatment of PE was confirmed by either of these studies.[5,26]

Another study that using tinzaparin looked at 432 patients with symptomatic DVT.[17] The patients were randomized to receive either tinzaparin or UFH. Patients were excluded from the study for the following reasons: acute bleeding or bleeding disorders; pregnancy; allergy to heparin, bisulfites, or fish; two or more previously documented episodes of PE or DVT; a history of protein C defiency; a history of heparin-associated thrombocytopenia; severe malignant hypertension (HTN); severe hepatic failure; or severe renal failure needing dialysis. All of the patients underwent baseline lung scanning, and 200 were found to have high-probability scans. Only 28 of those patients had any symptoms of PE. Of those 28, only 13 were randomized to receive LMWH.[17,36] The patients in the LMWH group were hospitalized as long as the UFH group. The author concluded that tinzaparin once per day was no less effective—and probably more effective—than use of dose-adjusted intravenous UFH for preventing recurrent VTE in patients with DVT and associated PE. The heparin was not dosed in a weight-related fashion, whereas the LMWH was weight-dosed. This is not a result that can be generalized to symptomatic patients with PE.

Another study evaluated the safety of outpatient treatment of PE with LMWH.[37] It is a small study, only 108 patients were followed for at least partial outpatient treatment. The 50 patients who had PE and were excluded had one of the following exclusion criteria:

- another medical condition requiring admission;
- active bleeding or a high risk of major bleeding;
- hemodynamic instability;
- pain requiring parenteral narcotics;
- requirement for O_2 to keep O_2 saturation above 90%;
- age younger than 18 years; or
- likelihood of poor compliance.

Table 3. Low Molecular-Weight Heparins

LMWHS	MW	HALF-LIFE	DOSING FOR INPATIENT TREATMENT OF DVT WITH OR WITHOUT PE
Ardeparin	6000	3.3	
Dalteparin	5000	2.7	
Enoxaparin*	4500	4.5	1.0 mg/kg q12h or 1.5 mg/kg qd
Nadroparin	4500	2.7	
Reviparin	4000	1.8	
Tinzaparin	4500	1.8	

*Enoxaparin is the only LMWH presently approved for certain low-risk patients, mostly those with asymptomatic PE in the presence of concomitant DVT. The U.S. Food and Drug Administration has approved two doses.[31]

Key: LMWH = low molecular weight heparin; PE = pulmonary embolism; DVT = deep vein thrombosis; MW = molecular weight

Table 4. Contraindications to Heparin Use

ABSOLUTE CONTRAINDICATION

- Active bleeding
- Cardiopulmonary instability
- Hereditary bleeding disorder
- Allergy to heparin
- History of heparin-induced thrombocytopenia

RELATIVE CONTRAINDICATION

- Hereditary or acquired thrombotic disorder
- Peptic ulcer disease, gastrointestinal/genitourinary bleeding < 6 weeks
- Renal insufficiency (CrCl < 30mL/min)
- Pulmonary embolism (hemodynamically unstable)

Researchers found a recurrent event rate of 5.6%, which is similar to other studies treating PE with LMWH.[5,26,37] The truly ill patients with PE, however, were excluded from the study as they met the exclusion criteria.

As tempting as it may be to pursue the thought of outpatient treatment of PE with the LMWHs, the data do not yet demonstrate that it is a safe way to treat those with symptomatic PE. The FDA has approved two LMWHs for outpatient treatment of acute DVT without PE as a bridge to wafarin.[36] Enoxaparin is approved for the treatment of DVT with or without PE on an inpatient basis.[38] The strategies of either an abbreviated hospital stay or treatment with LMWHs for symptomatic PE, however, remain without FDA approval.[36]

Thrombolysis in PE. Thrombolysis is a powerful tool in the treatment of patients with PE. *(See Table 5.)* If successfully used, it reverses right heart failure rapidly and safely in the appropriate patient.[36] Unfortunately, due to the lack of large randomized trials, the effectiveness of this treatment in increasing survival in patients with PE is not nearly as certain as thrombolysis in MI. It usually is far more difficult to diagnose with certainty that a patient in shock has PE. The indications for giving thrombolysis and the odds of successful outcome are much better studied in MI because it is an easier diagnosis to make and, therefore, to study in the acute setting. Yet, our premortem diagnosis and treatment of those with PE remains lower than that demonstrated at autopsy.[39-42] In fact, only about one-third of patients who die of PE have the correct premortem diagnosis.[40]

Thrombolytics have the ability not merely to limit further clot propagation, as do the heparins, but also to dissolve clots. Twelve hours after treatment with thrombolytics, there is a large decrease in right ventricular strain as compared to treatment with heparin. The difference seen on echo between the two treatment groups disappears after a week.[43] This clearly appears to be an advantage when the clot is in a position where timely removal can create differences in outcome. Use of thrombolytics in patients with PE demonstrates rapid improvement in hemodynamic measurements and pulmonary perfusion.[44] Right ventricular function recovers quickly after thrombolysis.[45] There is a more rapid decrease in pulmonary hypertension.[45] A difference in the long-term mortality rate or the recurrence of PE has not been demonstrated, although it may exist.[44]

Of course, for every treatment there is risk as well as benefit. *(See Tables 6 and 7.)* The increase in the speed of resolution of the clot lysis is offset by the increased risk of bleeding among those who receive thrombolytics. In the MAPPET trial, it was found that the patients who received thrombolytics had a 21.9% rate of major bleeding complications as opposed to 7.8% in the group who received heparin.[46] In other trials, the risk of major bleeding in those treated with thrombolytics was found to be 5-10%, with the risk of an intracranial bleeding found to be about 1-2%.[44,47-49] The risk of major bleeding with heparin treatment generally is about 4%.[14]

Another risk of using thrombolytics is that as the large clot lyses, it can move on to occlude other areas. This has been noted in those who have mobile right atrial thrombi. After thrombolysis, the atrial thrombosis is resolved, but new perfusion defects are noted on ventilation/perfusion scans.[50]

In thinking of those who have PE, it is useful to consider them in three categories of illness.[51] The first group of patients presents in shock. The second group of patients is symptomatic but has normal hemodynamic parameters and normal right ventricular pressures. Finally, the third group is composed of those who have normal clinical hemodynamic parameters but, when studied, are found to have signs of right ventricular overload.

The treatment of the first two groups generally is agreed upon. A 1995 study of a small group of patients who presented in shock due to PE demonstrated that none of the patients receiving thrombolysis died but all who received heparin died.[52] Only eight patients were studied because the trial was terminated when the results of the first eight were found to be so dramatic. For patients who present in shock, and therefore, demonstrate a high-

Table 5. Thrombolytics Dosing

MEDICATION	DOSING
Streptokinase	250,000 U IV (loading dose over 30 min); then 100,000 U/hr for 24 hr
Urokinase	2000 U/lb IV (loading dose over 10 min); then 2000 U/lb per h for 12-24 hr
Tissue plasminogen activator (t-PA)	100 mg IV over 2 hr
Tenecteplase	Weight-based dosing
Retavase	10 U and 10 U in 30 min

Table 6. Absolute Contraindications to Thrombolytics

- History of cerebrovascular accident
- Active gastrointestinal bleed
- Recent central nervous system surgery (< 2 months)
- Bleeding diathesis

Table 7. Relative Contraindications to Thrombolytics

- Recent major surgery (CABG, OB delivery, organ biopsy) within previous 10 days
- CVA disease
- Recent GI or GU bleeding
- Recent trauma
- HTN: Systolic > 180 and/or diastolic > 110
- Mitral stenosis or Afib (because of increased risk of LV heart thrombus)
- Acute pericarditis
- Subacute bacterial endocarditis
- Hepatic or renal disease causing hemostatic defect
- Hepatic failure
- Pregnancy
- DM—hemorragic retinopathy
- Septic thrombophlebitis or occluded AV cannula at infected site
- >75 yrs old if on oral AC

Key: CABG = coronary artery bypass graft; AC = anticoagulant; AV = aortic venous; DM = diabetes mellitus; HTN = hypertension; CVA = cerebrovascular accident; OB = obstetric; GU = genitourinary; GI = gastrointestinal; LV = left ventricular

er risk of mortality, the risk of bleeding is offset by the benefit of rapid clot lysis. Patients this ill cannot tolerate the workup often required to diagnose PE. A bedside echocardiogram often can be helpful in determining whether there is right heart strain or failure, and therefore, a high likelihood that PE is the cause of shock. In the appropriate clinical scenario, echo may be the best exam available to guide the practioner in choosing to use thrombolytics for the treatment of suspected massive PE.[53,54] It must be remembered that transthoracic echo fails to identify 50% of patients with angiographically proven PE; echo is merely a tool, not a gold standard.[55] Treatment with thrombolytics is most effective when there is a sudden onset of symptoms, although treatment with thrombolytics can be effective even after a delayed presentation.[56]

The second group of patients, those who are hemodynamically stable with no signs of right heart strain noted on study, is treated best with heparin. The increased risk of major bleeding that occurs with thrombolysis generally is felt to be unwarranted among this group. Heparin provides resolution of the clot in an adequate time frame.

There is controversy regarding thrombolytics in the decisions to treat the third group of patients who occupy the clinical middle ground.[44] They are not so sick as to be in shock, yet they have right ventricular (RV) strain that can be detected by echocardiogram. This group comprises about 40% of normotensive patients with acute PE.[57,58] It had been presumed that the RV strain demonstrated increases clot load, but another study found that RV dysfunction did not correlate with perfusion abnormalities on ventilation/perfusion scan.[60] Nonetheless, mortality among this group is high. In the MAPPET study, 8% of those who were normotensive but demonstrated RV strain on echo died.[53,59] The members of this group have been described as having "impending hemodynamic instability."[23] Significant studies have led some researchers to conclude that thrombolysis in this group is of enough benefit to warrant the extra bleeding risk.[53,61,62] Yet a study from 2001 has concluded that the patients in this group do not fare better clinically after treatment and they suffer from a higher complication rate due to bleeding than the patients treated with anticoagulation alone.[61] All of these studies were registry studies and have the limitations imposed by such a structure. As yet, there is no randomized controlled study available to answer this question.

In summary, thrombolytics have been shown to be beneficial in patients with PE who are in shock. In PE patients who are normotensive and have normal right ventricular pressures, the benefit of treatment with thrombolytics instead of anticoagulation is not enough to outweigh the risk of complications from thrombolytics. Anticoagulation should be used in these patients. The treatment of patients who are normotensive yet demonstrate right ventricular strain is controversial, with some advocating treatment with thrombolytics and some stating that there is no added benefit of thrombolytics over anticoagulation.

Embolectomy. Embolectomy can be performed either as an open surgical procedure or by a fragmentation and suction method in a closed percutaneous procedure using special apparatus. Patients who do not become hypotensive uniformly fare better without surgery, as long as further embolization can be prevented.[4] Patients who meet the current indications for embolectomy include patients who fail thrombolysis, patients who are too ill to attempt thrombolysis, and patients with contraindications to thrombolysis.[1]

Surgical embolectomy first was performed more than 75

years ago.[63] At that time, bypass was not available. Some still advocate a similar procedure done without bypass. Clarke and Abrams reported on their 25 years of experience, having done 55 embolectomies during that time. They utilize a short period of normothermic cardiac standstill after clamping both vena cava.[64] Those patients who had a cardiac arrest prior to the procedure predictably did worse than those who did not. Eighty percent of 19 patients who had arrested prior to the procedure died. The mortality rate for the 36 patients who had not arrested, however, was only 20%.[64] This demonstrates that even in institutions without bypass facilities, a surgical remedy is possible for those who are in dire straits.

Mortality rates among those utilizing bypass during the embolectomy range from 20-40%.[66-69] The patients who entered the studies were considered to be too ill for a trial of thrombolysis, failed thrombolysis, or had contraindications to thrombolysis.[65] Partial cardiopulmonary bypass (extracorporeal membrane oxygenation, or ECMO) also is an option to consider for open embolectomy.[70]

Percutaneous routes also are available to remove an embolus. Catheters can be placed that mechanically break up the clot and then suction the pieces.[71,72] Another option is to place a catheter percutaneously and then use it as a vehicle to directly introduce thrombolytics in close proximity to the pulmonary artery.[73] These are reasonable options in those found to have large, central clot load who are not candidates for systemic thrombolytic therapy.

It is important to consider ahead of time what route your institution is able to follow in patients who are not candidates for thrombolysis but who have severe disease due to PE. It is hoped that these patients are a rare occurrence, but when they do come to the ED, it is very important to mobilize as quickly as possible. A prepared protocol may save essential time.

Warfarin. After initial anticoagulation is achieved with heparin, long-term anticoagulation with warfarin should begin.[4] Warfarin should be started within three days of initial heparin therapy, as delayed schedules are associated with increases in hospital stay and slightly higher rates of recurrence.[10,74] The first 24 hours of warfarin therapy are associated with a transient hypercoagulable state, and heparin should not be discontinued until the international normalized ratio (INR) has been in the therapeutic range for at least two days.[11] Treatment with heparin and warfarin typically overlaps for five days to successfully bypass the transient rise in hypercoagulability.

The optimal duration of therapy with oral anticoagulation is uncertain.[76] The American College of Chest Physicians in 1998 called for at least three months of oral anticoagulant therapy after PE or DVT unless contraindicated.[11,12] Others have shown that six months of therapy are better than six weeks.[78-80] A study of 897 patients (107 with PE) randomized to six weeks or six months of therapy found that the former group had twice as many episodes of recurrence with no difference in rates of major hemorrhage.[78] For patients with a low risk of recurrence and temporary risk factors, three months of treatment seems to be sufficient. For patients with idiopathic venous thromboembolism or permanent risk factors who have a high risk of recurrence, other trials are necessary to assess prolonged therapy beyond six months.[81]

The research committee of the British Thoracic Society studied 712 patients with venous thromboembolism randomized to four weeks or three months of therapy. They found that patients treated for three months had significantly fewer recurrence episodes and failures of disease resolution than those treated for a shorter period of time.[82] However, they also found that the subgroup of patients with postoperative DVT and PE had a low rate of treatment failures and recurrence rates (3%), with no difference between the four-week and three-month therapy groups. They recommended only four weeks of anticoagulation (AC) for these patients.

Once the time period of treatment is determined, it is essential to consider the other obstacles to ongoing treatment. Among those patients age 65 and older who were hospitalized in New Jersey between January 1991 and June 30, 1994, and who actually began treatment for DVT or PE, 23% received therapy for less than the recommended length of time after hospital discharge. African-Americans were more likely to have a shorter than recommended length of treatment.[77] It is unclear why they had a higher rate of failure to complete treatment.

Inferior Vena Caval Filters. Inferior vena caval interruption filters are not a replacement for adequate anticoagulation.[4] The filters are inserted via the internal jugular vein or the femoral vein and positioned just below the renal vessels. The filters are supposed to catch large clots originating in the legs before they get to the pulmonic vessels. Unfortunately, there are various ways that they can fail. The filters can be positioned inadequately so that clots pass by them. Over time, collateral circulation can develop, permitting another route for the passage of clots. Rarely, clots may occlude the filter, causing caval thrombosis. Clots also may originate above the filter. Of course, a caval filter does nothing to treat the initial PE, so a method of emergent treatment must be considered as well.

There are two indications for the use of the caval filters.[1] One indication is that the patient has a contraindication to anticoagulation, and the second is that treatment with anticoagulation has failed.[4] Absolute contraindications to anticoagulation include active bleeding, neurological trauma, or surgery within the past week.[1] There are many other lesser contraindications, but they can be weighed against the need for anticoagulation vs. a filter, and often will be found to be less of a risk.

In patients who have an apparent failure of anticoagulation, it is imperative to determine whether the entire period of treatment has been at therapeutic levels. It is understandable that although a medication that must be taken religiously to maintain appropriate blood levels, patients occasionally may miss a dose. If this is the case, then anticoagulation has not failed; what has failed is adherence to the treatment regimen.

DVT does not occur only in the lower extremity. Patients with central venous lines or patients at high risk for clotting easily can have upper extremity DVT. For the patients with an upper extremity DVT, it is possible to place a superior vena caval filter.[83]

Table 8. Prevention of DVT and PE

Major abdominal surgery	LMWH (enoxaparin sodium, 30 mg BID, dalteparin sodium, 2500 U) Low-dose UFH (therapeutic dose q8 h, initiated during hospitalization) Intermittent pneumatic compression (initiated during hospitalization)
Total hip replacement	LMWH (therapeutic dose initiated during hospitalization) Warfarin (therapeutic dose initiated during hospitalization) Adjusted-dose UFH (therapeutic dose initiated during hospitalization)
Hip fracture repair	LMWH Warfarin
Total knee replacement	LMWH Intermittent pneumatic compression

Key: LMWH = low molecular weight heparin; UFH = unfractionated heparin

Prevention

It has long been known that those who are bed-bound or immobilized for a period of time are at higher risk for thromboembolism. Patients who undergo major orthopedic procedures are at particularly high risk of developing venous thromboembolism. Without heparin prophylaxis, 48% of those patients will develop DVT.[82,84] PE is the third most common cause of death in trauma patients who survive more than 24 hours.[86] Medical patients who are limited in their movements also are prone to venous thromboembolic disease.[87] Others at high risk include patients with disseminated malignancy, CHF, recent stroke, and previous venous thromboembolism.[88]

There are multiple ways to address prophylaxis for venous thromboembolism in the hospitalized patient. Traditional choices for prevention include the use of low-dose UFH given subcutaneously two or three times per day at a dose of 5000 units, intermittent pneumatic compression, elastic stockings, warfarin, or a combination of these options. *(See Table 8.)* LMWHs also are a choice in prevention.[85] It has been shown that prophylactic treatment with the LMWH enoxaparin at 40 mg per day subcutaneously safely reduces the risk of venous thromboembolism in patients with acute medical illness.[87] One researcher used reviparin once daily to effectively decrease DVT in casted and, therefore, immobilized patients. No patients taking the LMWH developed PE, but 2/188 patients in the placebo group developed PE.[89] LMWHs also have been shown to be more effective than UFH in preventing VTE in patients at especially high risk.[91]

Aspirin at a dose of 160 mg a day reduces the risk of PE and DVT by at least one-third during a period of increased risk (orthopedic surgery), and there now is good evidence for considering aspirin routinely in a wide range of surgical and medical patients at high risk of venous thromboembolism,[92] although other methods may be more effective.[85]

The decision regarding venous thromboembolic prophylaxis may be left to the admitting physician, but a reminder from the emergency physician about the necessity of prophylaxis might be helpful. Indeed, in these days of increased ED congestion as patients wait for inpatient beds, it behooves the ED physician to at least consider instituting prophylaxis for appropriate patients in the ED. Thromboembolic disease is a high stakes illness, and prevention can begin in the ED.

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Physician CME Questions

111. The differential diagnosis of pulmonary embolism *does not* include which of the following?
    A. Sepsis
    B. Myocardial infarction
    C. Pneumothorax
    D. Thrombocytopenia purpura

112. It is important to get an ECG on a patient who is suspected of having a pulmonary embolism because:
    A. It is important to screen for other illnesses in a patient who is suspected of having a PE.
    B. The S1Q3T3 pattern often is seen and is diagnostic of PE.
    C. All patients with PE have tachycardia.
    D. A normal ECG means a patient does not have a PE.

113. Of patients who present with PE, which of the following is true?
    A. All are extremely ill and easily diagnosed clinically.
    B. Eight percent present in extremis.
    C. Ninety percent present without any symptoms.
    D. Few have previous clots in either the lung or the legs diagnosed.

114. Which of the following is *not* an acceptable treatment for PE?
    A. Vena caval interruption filters
    B. Pneumonectomy
    C. Thrombolysis
    D. Anticoagulation with heparin

115. Since the 1930s, acute treatment for PE has been based on:
    A. thrombolysis.
    B. embolectomy.
    C. anticoagulation.
    D. low molecular weight heparin.

116. Thrombolysis should *not* be used in which of the following?
    A. A patient with an active gastrointestinal bleed
    B. A patient with a history of a cerebrovascular accident
    C. A patient with bleeding diathesis
    D. All of the above

117. Which of the following statements is true regarding low molecular-weight heparin and unfractionated heparin?
    A. They are administered in the same way.
    B. They have the same half-life in the body.
    C. They cost the same.
    D. They both carry a risk of bleeding.

118. Which of the following is an advantage of unfractionated heparin?
    A. It stops working soon after the intravenous infusion is stopped.
    B. Few tests are needed to evaluate its efficacy.
    C. It never causes major bleeding episodes.
    D. It can be given once per day.

119. Which of the following statements is true of low molecular-weight heparin?
    A. It can be administered through a transdermal patch.
    B. It is approved by the FDA to treat all PEs.
    C. It can be used to treat DVTs.
    D. It requires frequent blood tests to evaluate efficacy.

120. Relative contraindications to thrombolysis include which of the following?
    A. CVA disease
    B. Active GI bleeding
    C. Hepatic failure
    D. Pregnancy
    E. All of the above

Answer Key:

111. D	116. D
112. A	117. D
113. B	118. A
114. B	119. C
115. C	120. E

Emergency Medicine Reports
CME Objectives

To help physicians:

- quickly recognize or increase index of suspicion for specific conditions;
- understand the epidemiology, etiology, pathophysiology, and clinical features of the entity discussed;
- apply state-of-the-art diagnostic and therapeutic techniques (including the implications of pharmaceutical therapy discussed) to patients with the particular medical problems discussed;
- understand the differential diagnosis of the entity discussed;
- understand both likely and rare complications that may occur.

Emergency Medicine Reports
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Pulmonary Embolism, Part II

Differential Diagnosis of Patient with Symptoms of Pulmonary Embolism

- Shock—cardiogenic, septic, neurogenic, anaphylactic, hemorrhagic
- Aortic dissection
- Pneumonia
- Pleurisy
- Pneumothorax
- Asthma
- Congestive heart failure
- Pericarditis
- Acute myocardial infarction
- Other emboli (i.e., fat, air, amniotic fluid, bullet)
- Anxiety attack
- Musculoskeletal pain
- Costochondritis
- Metabolic acidosis
- Angina

Low Molecular-Weight Heparins

LMWHS	MW	HALF-LIFE	DOSING FOR INPATIENT TREATMENT OF DVT WITH OR WITHOUT PE
Ardeparin	6000	3.3	
Dalteparin	5000	2.7	
Enoxaparin*	4500	4.5	1.0 mg/kg q12h or 1.5 mg/kg qd
Nadroparin	4500	2.7	
Reviparin	4000	1.8	
Tinzaparin	4500	1.8	

*Enoxaparin is the only LMWH presently approved for certain low-risk patients, mostly those with asymptomatic PE in the presence of concomitant DVT. The U.S. Food and Drug Administration has approved two doses.[31]

Key: LMWH = low molecular weight heparin; PE = pulmonary embolism; DVT = deep vein thrombosis; MW = molecular weight

Low Molecular-Weight Heparin vs. Unfractionated Heparin

	ADVANTAGES	DISADVANTAGES
Low molecular-weight heparin	• Can be given via subcutaneous shot instead of intravenously. • Dosing is less frequent • Very effective treatment for many DVTs	• Not yet shown to be safe treatment for all patients with PE. • High cost • Bleeding risk
Unfractionated heparin	• Historically well-demonstrated to be an effective treatment for PE when dosed appropriately • Effect can be stopped quickly once the IV infusion is turned off. • Less expensive	• Requires many blood draws and lab work to make sure dose is appropriate. • Bleeding risk

Contraindications to Heparin Use

ABSOLUTE CONTRAINDICATION

- Active bleeding
- Cardiopulmonary instability
- Hereditary bleeding disorder
- Allergy to heparin
- History of heparin-induced thrombocytopenia

RELATIVE CONTRAINDICATION

- Hereditary or acquired thrombotic disorder
- Peptic ulcer disease, gastrointestinal/genitourinary bleeding < 6 weeks
- Renal insufficiency (CrCl < 30mL/min)
- Pulmonary embolism (hemodynamically unstable)

Thrombolytics Dosing

MEDICATION	DOSING
Streptokinase	250,000 U IV (loading dose over 30 min); then 100,000 U/hr for 24 hr
Urokinase	2000 U/lb IV (loading dose over 10 min); then 2000 U/lb per h for 12-24 hr
Tissue plasminogen activator (t-PA)	100 mg IV over 2 hr
Tenecteplase	Weight-based dosing
Retavase	10 U and 10 U in 30 min

Relative Contraindications to Thrombolytics

- Recent major surgery (CABG, OB delivery, organ biopsy) within previous 10 days
- CVA disease
- Recent GI or GU bleeding
- Recent trauma
- HTN: Systolic > 180 and/or diastolic > 110
- Mitral stenosis or Afib (because of increased risk of LV heart thrombus)
- Acute pericarditis
- Subacute bacterial endocarditis
- Hepatic or renal disease causing hemostatic defect
- Hepatic failure
- Pregnancy
- DM- hemorragic retinopathy
- Septic thrombophlebitis or occluded AV cannula at infected site
- >75 yrs old if on oral AC

Key: CABG = coronary artery bypass graft; AC = anticoagulant; AV = aortic venous; DM = diabetes mellitus; HTN = hypertension; CVA = cerebrovascular accident; OB = obstetric; GU = genitourinary; GI = gastrointestinal; LV = left ventricular

Absolute Contraindications to Thrombolytics

- History of cerebrovascular accident
- Active gastrointestinal bleed
- Recent central nervous system surgery (< 2 months)
- Bleeding diathesis

.

Prevention of DVT and PE

Major abdominal surgery	LMWH (enoxaparin sodium, 30 mg BID, dalteparin sodium, 2500 U) Low-dose UFH (therapeutic dose q8 h, initiated during hospitalization) Intermittent pneumatic compression (initiated during hospitalization)
Total hip replacement	LMWH (therapeutic dose initiated during hospitalization) Warfarin (therapeutic dose initiated during hospitalization) Adjusted-dose UFH (therapeutic dose initiated during hospitalization)
Hip fracture repair	LMWH Warfarin
Total knee replacement	LMWH Intermittent pneumatic compression

Key: LMWH = low molecular weight heparin; UFH = unfractionated heparin

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